[LITERATURE REVIEW]

Optimizing Treatment Approaches in Seborrheic Dermatitis

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ABSTRACT

Seborrheic dermatitis is a chronic, recurring, cutaneous condition that causes erythema and flaking, sometimes appearing as macules or plaques with dry white or moist oily scales. In adults, it commonly occurs in areas with high concentrations of sebaceous glands. The face and scalp are the most frequently affected areas, and involvement of multiple sites is common. Dandruff is regarded as a mild noninflammatory form of seborrheic dermatitis. There is a high incidence of seborrheic dermatitis among persons with human immunodeficiency virus infection or Parkinson's disease. The cause of seborrheic dermatitis is not well understood, but appears to be related to the composition of the sebaceous gland secretions, the proliferation of *Malessezia* yeasts, and the host immune response. Treatment options for nonscalp and scalp seborrheic dermatitis include topical agents and shampoos containing antifungal agents, anti-inflammatory agents, keratolytic agents, and calcineurin inhibitors. Because multiple body sites are usually involved, the physician should examine all commonly affected areas. Patients should be made aware that seborrheic dermatitis is a chronic condition that will probably recur even after successful treatment. (*J Clin Aesthet Dermatol.* 2013;6(2):44–49.)

Seborrheic dermatitis (SD), a chronic, recurrent, inflammatory condition characterized by erythema and skin flaking, may be resistant to treatment and often has a substantial negative impact on quality of life.[1–3] It affects approximately six million people in the United States and is associated with direct and indirect medical costs of approximately $230 million per year.[4]

Although the causes of SD are not completely understood, progress has been made in this area, and several effective treatment options are available. This article will review the clinical presentation of SD and the current understanding of its etiology and discuss currently available treatment options.

CLINICAL PRESENTATION

Seborrheic dermatitis may appear as macules or thin plaques with a reddish or yellow appearance and dry white or moist oily scales.[5] In adults, it most often occurs in areas with a high concentration of sebaceous glands, including the face, scalp, ears, chest, and body folds.[5] It usually affects multiple body areas, occurring on the face in 88 percent of patients, the scalp in 70 percent, the chest in 27 percent, and the arms or legs in 1 to 2 percent.[3] In more than half of patients with facial SD, the scalp is affected as well.[3] On the face, SD commonly occurs in the nasolabial folds, eyebrows, anterior hairline, and glabella.[1,6] On the scalp, the lesions may range from mild desquamation to brownish crusts affixed to the skin and hair.[5] Lesions on the central chest may have a petaloid appearance.[7] Some patients report pruritus, particularly if the scalp is affected.[2,5,6] It generally is not accompanied by papules or pustules.[2] Secondary bacterial infection may occur, aggravating erythema and exudate and causing local discomfort.[5]

In adults, SD is a chronic, recurrent condition marked by periods of exacerbation occurring at variable intervals.[6] Patients may report that outbreaks are triggered by emotional stress, depression, fatigue, exposure to air conditioning or damp or dry conditions in the workplace, systemic infections, use of certain medications, or other factors.[3]

The infantile form of SD is a self-limited condition generally resolving by age three or four months.[6] The adult form usually appears first around the time of puberty, when sebaceous glands become more active, sometimes lasting until young adulthood.[1] The condition increases

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again in prevalence after age 50.[1] It affects approximately 1 to 5 percent of immunocompetent adults and as many as 20 to 83 percent of human immunodeficiency virus (HIV)-positive individuals.[5,6] Other populations at risk include persons with Parkinson's disease or other neurological disorders, mood disorders, significant life stress, or low exposure to sunlight.[2] More men than women have SD, but it shows no preference for any racial or ethnic group.[6] It may occur in association with atopic dermatitis or other skin disorders, complicating its diagnosis.[8]

Some controversy has surrounded the relationship between SD and dandruff. Most authors now agree that dandruff is a mild, noninflammatory form of SD.[2,6,9] Dandruff is extremely common, with a prevalence as high as 50 percent of the population.[2]

CAUSES OF SEBORRHEIC DERMATITIS

Although the causes of SD are not completely understood, it appears to result from a combination of the following three factors: sebaceous gland secretion, presence of *Malassezia* yeast, and the host immune response.[6]

Sebum is an important component of skin surface lipids and contains high amounts of squalene, wax esters, and triglycerides.[10] Persons with SD do not necessarily have excess sebaceous gland activity, but the composition of their skin surface lipid may be altered, creating a more supportive environment for growth of lipid-dependent micro-organisms.[10]

The role of *Malassezia* yeasts in SD is somewhat controversial, although most researchers believe they play an important role.[9] *Malassezia* yeasts are normally commensal species found primarily in follicular infundibula and commonly isolated from sebum-rich areas of the body, such as the face, scalp, trunk, and back.[11] They produce abundant lipases that hydrolyze triglycerides and free saturated fatty acids on which the yeast is dependent.[12] These fatty acids may have irritant effects that induce scaling or may cause release of arachidonic acid, which promotes inflammation in skin.[9] There are seven primary species: *M. globosa, M. restricta, M. obtusa, M. slooffiae, M. sympodialis, M. furfur,* and *M. pachydermatis* (the last occurs only on animals).[9] *M. globosa* and *M. restricta* are thought to be the species most commonly associated with SD, although *M. furfur* and other species have also been implicated.[9,13,14] Some studies have found high numbers of *Malassezia* yeasts on the scalp of persons with SD, but others have found no difference in the density of these yeasts between the skin of persons with SD and that of persons without it.[1] Differing sampling methods may contribute to these contradictory findings. *Malassezia* exist not only on the skin surface, but also within the layers of the stratum corneum, and a true count would require examining the full thickness of the skin squama.[1] Support for the role of *Malassezia* in SD comes from studies demonstrating that use of various antifungal treatments results in reduction of *Malassezia*, which is accompanied by improvement in symptoms.[6,9]

The role of the host immune response in the pathogenesis of SD is uncertain. Some researchers have reported increased numbers of natural killer cells, CD16 cells, and inflammatory interleukins and activation of complement in the lesional skin of patients with SD compared with their own nonlesional skin or the skin of healthy controls.[6] Nevertheless, total antibody levels are no higher in SD patients than in controls and a host response specific to *Malassezia* yeasts has not been identified.[9] The prevalence of SD in persons infected with HIV suggests that the condition is mediated by the immune system; however, the response of SD to successful retroviral therapy is variable.[5]

Thus, a definitive understanding of the pathophysiology of SD awaits further research, but the role of *Malassezia* yeasts as causative or contributing agents appears to be well established.

DIAGNOSIS

The differential diagnosis of SD should include psoriasis, rosacea, *Demodex* dermatitis, atopic eczema, pityriasis versicolor, contact dermatitis, and tinea infections.[2] SD may also resemble Langerhans cell histiocytosis or secondary syphilis.[2,5] The diagnosis is usually clinical, but candidiasis, tinea infection, and *Demodex* dermatitis may be ruled out with a negative potassium hydroxide test.[2] It should be kept in mind that SD may be accompanied by other dermatological disorders.

Care should be taken to differentiate SD from psoriasis vulgaris.[15] Early SD has a spongiform appearance that distinguishes it from psoriasis, but in later stages these conditions are more difficult to tell apart. Some patients present with sebopsoriasis, which includes features of both disease states.[2] Lesions on the elbows or knees and nail pitting suggest psoriasis, which may spare the face.[15]

TREATMENT

The primary goals of therapy for SD are to clear the visible signs of disease and reduce bothersome symptoms, especially pruritus.[6] Because the face and scalp are the most commonly affected areas, itching or redness on the scalp in a patient with facial SD indicates the need for treatment at both sites.[3] Patients should be informed that SD is a chronic, relapsing condition and that they should anticipate future outbreaks.[16] Patients should also be advised to avoid triggers of SD symptoms to the extent possible and not to irritate the lesions by excessive scratching or use of potent keratolytic preparations.[16,17]

NONSCALP SEBORRHEIC DERMATITIS

Antifungal agents, anti-inflammatory agents, and keratolytic agents are available in a variety of formulations for treatment of SD on areas other than the scalp. Table 1 lists commonly used treatments for nonscalp SD and indicates the level of evidence that supports their use.

Antifungal agents. With the understanding of the role of *Malassezia* in SD, antifungal agents have taken on an important role in its treatment. Ketoconazole 2% cream

TABLE 1. Treatments for nonscalp seborrheic dermatitis

	LEVEL OF EVIDENCE*
ANTIFUNGAL AGENTS	
Ketoconazole	A
Ciclopiroxolamine	A
Sertaconazole	C
Metronidazole	A
Itraconazole (oral)	C
Lithium succinate/lithium gluconate	A
CORTICOSTEROIDS	
Hydrocortisone	A
ANTI-INFLAMMATORY/ANTIFUNGAL COMBINATION	
Promiseb® Topical Cream	B
CALCINEURIN INHIBITORS	
Tacrolimus	B
Pimecrolimus	B

*Levels of evidence: A=randomized, double-blind, controlled trial(s); B=randomized single-blind trial(s); C=open-label studies

applied twice daily for four weeks has been shown to be as effective as hydrocortisone 1% cream in treatment of SD at multiple body sites.[18] In a randomized, double-blind trial of 459 patients with SD treated with ketoconazole 2% gel or vehicle once daily for 14 days, there was a significantly higher rate of successful treatment (25.3% vs. 13.9%, P=0.0014) and significantly greater reductions in erythema, pruritus, and scaling in ketoconazole-treated patients.[19] A 2% foam formulation of ketoconazole has been shown to be significantly more effective than vehicle for treatment of SD on the face, scalp, and body, and equally as effective as ketoconazole 2% cream.[20]

Ciclopiroxolamine 1% cream, twice daily for 28 days followed by once daily for 28 days, was compared with vehicle for the treatment of SD in a randomized, double-blind trial that enrolled 129 patients.[21] At the end of the maintenance phase, complete disappearance of erythema and scaling was found in 63 percent of the ciclopiroxolamine-treated group and 34 percent of the vehicle-treated group (P<0.007).[21]

In an open-label study of sertaconazole nitrate 2% cream, 59 percent of 20 subjects with mild-to-severe SD were successfully treated, with improvements in scaling, erythema, induration, and pruritus.[22]

A randomized, double-blind study demonstrated that metronidazole 0.75% gel is as effective as ketoconazole 2% cream in treatment of facial SD, with a similar side effect profile.[23]

For patients with persistent SD resistant to topical agents, oral antifungals may be an option. Oral itraconazole given in a dose of 200mg/day for one week, followed by a maintenance dose, resulted in clinical improvement of SD symptoms in two open-label trials.[24,25]

Corticosteroids. Hydrocortisone and a wide variety of other low- to mid-potency corticosteroids have been used successfully in the treatment of SD. A double-blind study that compared hydrocortisone 1% cream with ketoconazole 2% cream in 72 patients with mild-to-moderate SD found that the two agents produced similar rates of response and similar reductions in scaling, redness, itching, and papules.[26] In a 12-week, single-blind, randomized, comparative trial, hydrocortisone 1% ointment was found to be equally as effective as tacrolimus 0.1% ointment in reducing the symptoms of facial SD by physician assessment, although tacrolimus was superior by patient assessment.[27]

Combination antifungal/anti-inflammatory. Promiseb® Topical Cream (Promius Pharma, LLC, Bridgewater, New Jersey) is a nonsteroidal prescription medical device with anti-inflammatory and antifungal activity approved for treatment of SD.[28] In an investigator-blind, parallel-group study, 77 patients with mild or moderate SD of the face were randomized to combination antifungal/anti-inflammatory cream or desonide 0.05% cream twice daily for up to 28 days.[29] Severity of symptoms declined significantly from baseline to Day 14 and Day 28 in both groups.[29] Treatment was successful (clear or almost clear) in 85 percent of patients using combination antifungal/anti-inflammatory cream and 92 percent of patients using desonide cream (P=not significant) and the two products had similar safety profiles.[29]

Calcineurin inhibitors. Topical calcineurin inhibitors have immunomodulatory and anti-inflammatory properties that make them useful in the treatment of SD.[27]

Tacrolimus 0.1% ointment was found to be as effective as hydrocortisone 1% ointment in the treatment of SD, required fewer applications during the 12-week study period because of clearing of symptoms, and was rated more favorably by patients.[27]

In a randomized, open-label trial, pimecrolimus 1% cream was compared with betamethasone 0.1% cream in 20 patients with SD who were instructed to discontinue treatment when symptoms cleared.[30] By Day 9, all patients had discontinued treatment.[30] The two drugs were equally effective at reducing symptoms of erythema, scaling, and pruritus, but symptom relief was sustained longer in the pimecrolimus group.[30] In comparative trials, pimecrolimus 1% cream has been shown to be as effective as hydrocortisone 1% cream and ketoconazole 2% cream in the treatment of SD, with higher rates of adverse effects.[31,32] Pimecrolimus 1% cream was found to be significantly more effective for treatment of facial SD than methylprednisolone 0.1% cream or metronidazole 0.75% gel when applied twice daily for eight weeks, with fewer adverse effects and a lower rate of recurrence than metronidazole.[33]

SCALP SEBORRHEIC DERMATITIS

Seborrheic dermatitis of the scalp is most conveniently treated with shampoos containing antifungal agents, corticosteroids, or keratolytic agents; products are also available that combine drugs from these different classes. Table 2 lists commonly used treatments for SD of the scalp and indicates the level of evidence that supports their use.

Antifungal shampoos. Ketoconazole 2% shampoo was compared with selenium sulfide 2.5% shampoo in a four-week, randomized, double-blind trial of patients with moderate-to-severe dandruff.[34] Twice-weekly use of either shampoo was superior to placebo, but not significantly different from each other.[34] There was a significantly higher incidence of adverse effects among patients using selenium sulfide shampoo.[34]

Ciclopirox 1% shampoo used once or twice weekly for four weeks was shown to be superior to vehicle for treatment of SD in a randomized, double-blind, controlled study that recruited 949 patients.[35] Subsequent prophylactic use of ciclopirox shampoo once weekly or once every two weeks reduced the relapse rate.[35]

Ciclopirox shampoo and ketoconazole shampoo were compared in a double-blind study of 350 patients with SD.[36] The two treatments were equally effective and both better than placebo, although patients rated the ciclopirox shampoo more favorably.[36]

Corticosteroid shampoos. In a randomized, single-blind study of 326 subjects with moderate-to-severe scalp SD, clobetasol propionate 0.05% shampoo twice weekly for four weeks produced a significantly greater reduction in symptoms than ketoconazole 2% shampoo.[37] Alternating use of clobetasol shampoo and ketoconazole shampoo was also superior to ketoconazole shampoo alone.[37]

Combination products. Promiseb® Plus Scalp Wash (Promius Pharma, LLC) contains surfactants and skin conditioning agents, which remove excess sebum as well as lactoferrin and piroctone olamine, which may reduce the proliferation of *Malassezia*.[38] In an open-label trial, 25 subjects with SD used this proprietary wash an average of twice weekly for two weeks.[38] All 25 had a positive response and more than 90 percent reported improvement in seborrhea, dandruff, pruritus, and redness.[38]

In a single-blind study, a shampoo containing ciclopiroxolamine 1.5% and salicylic acid 3% was shown to have efficacy similar to that of ketoconazole 2% shampoo for the treatment of dandruff/SD.[39] For both groups, improvement was sustained for 14 days after treatment ended.[39]

A shampoo containing ciclopiroxolamine 1.5% and zinc pyrithione 1% was found to be as effective as ketoconazole 2% foaming gel in a single-blind study of 189 patients with scalp SD, with a greater reduction in pruritus during the early treatment phase and more favorable ratings from patients.[40]

Keratolytic products. A randomized, double-blind study compared a shampoo containing lipohydroxy acid 0.1% and salicylic acid 1.3% with a shampoo containing ciclopiroxolamine 1.5% and salicylic acid 3% in 100 subjects with scalp SD.[41] After four weeks of treatment, the tolerance, global efficacy, and cosmetic effects of the lipohydroxy acid shampoo were significantly superior to those of the ciclopiroxolamine shampoo.[41]

A topical solution of urea, propylene glycol, and lactic acid, applied daily for four weeks then three times per week for four weeks, was compared with placebo for treatment of mild-to-severe SD of the scalp.[42] Erythema and desquamation were improved at Weeks 2 and 4, but the improvements were not maintained at eight weeks.[42]

TABLE 2. Treatments for seborrheic dermatitis of the scalp

	LEVEL OF EVIDENCE*
ANTIFUNGAL AGENTS	
Ketoconazole shampoo	A
Ciclopiroxolamine shampoo	A
CORTICOSTEROIDS	
Clobetasol propionate	B
COMBINATION PRODUCTS	
Promiseb® Plus Scalp Wash	C
Ciclopiroxolamine/salicyclic acid	B
Ciclopiroxolamine/zinc pyrithione	B
KERATOLYTIC PRODUCTS	
Lipohydroxy acid	A
Propylene glycol	A

*Levels of evidence: A=randomized, double-blind, controlled trial(s); B=randomized single-blind trial(s); C=open-label studies

CONCLUSION

Seborrheic dermatitis is a common, chronic, inflammatory cutaneous condition characterized by erythema and skin flaking that tends to recur even after successful treatment and has a significant negative impact on quality of life. Its occurrence appears to be related to the proliferation of commensal *Malassezia* species. Occurrence at multiple body sites is common; the face and scalp are the most frequently affected areas. Numerous antifungal, anti-inflammatory, keratolytic, and immunomodulatory agents have been shown to be effective in the treatment of SD, but patients should be informed that recurrence is common and that ongoing treatment may be necessary.

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